University of Virginia

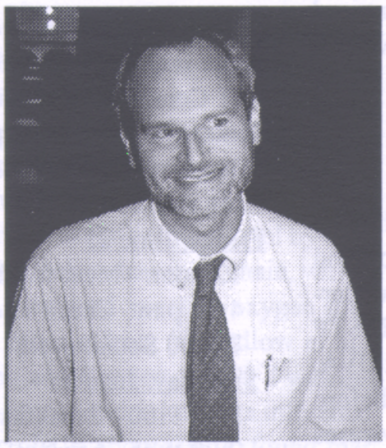
HEALTH
SCIENCES
CENTER

# M.D./Ph.D. Program Newsletter

Volume 1, No. 2 Spring 1999

## Alumni Focus

Dr. William A Petri, M.D., Ph.D., UVA Class of 1982 is currently a Professor of Medicine, Pathology and Microbiology at the University of Virginia. Among the many committees he chairs, Dr. Petri has continued to be an active member of the MD/PhD program. He is now the Associate Director of the MD/PhD Program Medical Curriculum Committee. Despite his busy schedule, we were lucky to reach him and get his perspective on being an MD., Ph.D. as our Alumni Focus for this issue.



William Petri, M.D., Ph.D.

**1. As an alumnus, how do you think the combined degree program here has changed since you were a student?**

When I started the program there was concern nationally about whether the NIH would continue to support MSTP training. UVA had just started an MSTP program but had not yet received an NIH grant. Within the Pharmacology Department (where the MSTP program was directed first by Bob Haynes and then by Al Gilman) there was strong support for the concept of MD-PhDs, but the more common situation was for some to question the value of such joint training. There were three MSTP students in my class, with the other two dropping out of the PhD portion after 2 years. We did not have any MSTP "programmatic" activities and little direction from the program, but I did know a few of the other students (including Tom Sturgill). I probably did well in the absence of much structure in the program because I had an excellent research advisor in Bob Wagner, who looked after, and continues to look after (!) my best interests. Even 20 year ago the Microbiology Department was flexible with its course work requirements for MSTP students, and besides some problems with Cot curves and one memorably disasterous immunology exam, graduate school went pretty smoothly. There was no mechanism to aid in the transition back to medical school, but my medical school classmates were a great help for the first couple of weeks back until I began to remember what to do.

Coursework was less intense during the first two years of medical school than it is now (one could complete gross anatomy during the summer before first year, and the basic science coursework ended in March of the second year), so I was able to spend a good deal of time in the lab before my time in graduate school officially started. This was part of the reason that I was able to finish the joint degree program (including 4th year electives) in 6 years.

**2. What are the future goals or the changes that you envision for the combined degree curriculum as our current Associate Director of the MD/PhD Program Medical Curriculum?**

I want to see how well the changes we instituted this year (substitution of graduate student cell and biochemisty for the medical school equivalents, and self-study histology) work before considering anything else. I see the molecular medicine course as an ideal setting for MD/PhD students to become exposed to clinically oriented basic research that they could pursue for their PhD degree. The trend needs to be towards decreased time in class for MD/PhD students, and I hope to see flexibility in coursework requirements for MD/PhDs become the rule at UVA. I believe that MD/PhD students who plan on doing a clinical residency need to take several months of 4th year electives (including an acting in-

> ***"The combination of the two careers is much more interesting and fun than either by itself".***

(Continued on page 2)

### In This Issue . . .

Alumni Focus....................................................p. 1-2
Summer Retreat at Smith Mtn. Lake.......................p. 2
Recent Publications ........................................p. 5-6
Student Focus ..................................................p. 3-4
Ph.D.s Received ...............................................p. 4
Research-In-Progress Dinners.............................. p. 5

## Alumni Focus (continued from page 1)

ternship) to be well prepared. We need to allow time for this by getting students embarked on their dissertation research as rapidly as possible.

**3. What do you think the roles of MD/PhD's will be in the future?**

Physicians are ideally suited to identify important questions in medicine; scientists have the tools and approaches to answer the questions. The MD/PhD graduate occupies the interface of medicine and science and is in the ideal situation to apply molecular approaches of research to important problems in human health. In my opinion there is no occupation more rewarding than clinical investigation. I am continually challenged and excited by my research, teaching and clinical practice. Every day is different and brings with it new things to learn and master.

**4. How did you become interested in your area of research?**

I was originally interested in cancer research, having worked at the National Cancer Institute in high school, and the McArdle Laboratory for Cancer Research as an undergraduate student at Wisconsin. When I started the MSTP program there was little in the way of cancer research at UVA, so my interests turned to virology. This was the time before molecular biology and monoclonal antibodies, where viruses were used as models to understand the more complex, and at the time unapproachable, workings of cells. After completing a residency in Internal Medicine, my work in virology led me to infectious diseases as a subspecialty. Amebiasis was an important area that was understudied and that was now (with the then new science of molecular biology) approachable to scientific investigation. I felt that I could help alleviate human suffering in the poor countries of the world, and at the same time do science on a fascinating eukaryotic organism.

My research program now spans the spectrum from clinical to basic investigation. My research group is conducting a new 4 year field study of amebiasis in children in a refugee camp in Bangladesh, developing an amebiasis vaccine through a program project involving UVA & Virginia Tech, studying at the cell biology and biophysical levels the mechanisms of adherence and killing of host cells by the parasite, and exploring the control of gene expression in Entamoeba histolytica. It is an exciting time in the lab as these different projects converge on a solution to this disease.

**5. How does your research inform your clinical work, and vice versa?**

Clinical work requires a broad perspective and knowledge base, whereas research requires an ability to focus on a single problem. The combination of the two careers is much more interesting and fun than either by itself. I think that my perspective as a clinician helps me from getting distracted by side issues in my research that are without clinical importance. My research training probably makes me more critical of the processes by which clinical decisiona are made. Research gives satisfaction over the long term, while taking care of patients and teaching give immediate emotional rewards. It is a privilege to be a scientist, physician and teacher!

# Summer Retreat

This summer, from June 25-27, M.D./Ph.D. Students will gather at the Smith Mountain Lake 4-H Center in beautiful Wirtz, Virginia. Students will have the opportunity to share scientific pursuits as well as to enjoy hiking, swimming and boating.

Friday, June 25

12 noon - Meet for departure from C'ville
4:30 p.m. Check into Smith Mtn.
7-9:00 Social event

Saturday, June 26

8:30-9:00 - Breakfast
9:00-9:45 - Student Talk -John Luckey
10-12:00 - Career Workshop
12:00 - Lunch
1-1:30 Student Talk -Robert Scoggins
1:30 Free time to enjoy the Lake
5:30 Dinner
7:30-midnight - Free time, social events

Sunday, June 27

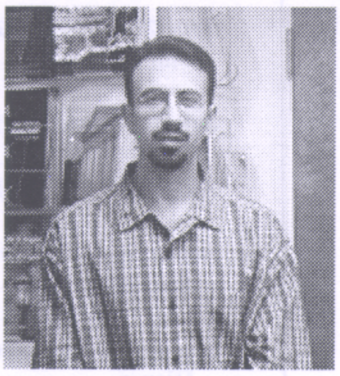
11:00 check out and return to C'ville

Faculty guests for Saturday's Career Workshop will include Dr. Pearson, Assoc. Dean of Medical Student Affairs, Dr. Dan Theodorescu, Dept. of Urology, and Dr. Coleen McNamara, Dept. of Internal Medicine, Division of Cardiology.

This Newsletter is published
twice a year.
Ideas and comments are welcome.

Rumey Ishizawar, Editor
ri4n@virginia.edu
Jane Cornelius
jcc5k@virginia.edu
804-924-1294
Contributing writers: Steve Cheung
Mike Nemergut

# Student Focus



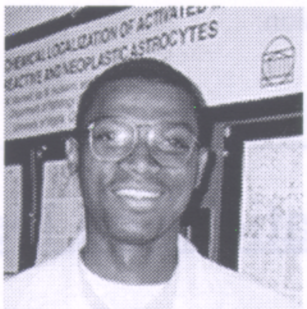
David Cassarino is currently completing his clinical clerkships. He recently received his Ph.D. in Neuroscience. His advisor is Dr. Jim Bennett.

### Mitochondrial Oxidative Pathology and Nuclear Responses in Neurodegenerative Disease Models.-

My project centered on the role of mitochondrial damage in neurodegenerative diseases including Parkinson's and Alzheimer's disease. Both of these diseases are characterized at the cellular level by biochemical defects in the electron transport chain, which are thought to lead to increased reactive oxygen species (ROS), amongst other effects (Swerdlow et al., 1996, 1997, Cassarino and Bennett, 1999). I was interested in how these mitochondrial defects influence the nucleus and their role in apoptosis. I found that cells transformed with disease mitochondria ("cybrids") respond by increasing the activities of their nuclear-encoded protective antioxidant enzymes. I also found similar changes in cells treated with the complex I inhibitor and parkinsonian neurotoxin MPP+ (the active metabolite of the toxin MPTP which was ingested by a group of California drug-users in the 1980s, giving them severe parkinsonism). To further explore the mechanisms by which mitochondrial oxidative pathology affects the nucleus, I examined the mitochondrial transition pore (MTP) in our model systems.

The MTP is thought to be a ubiquitous mediator of cell death, being activated by oxidative stress, electron transport chain inhibitors, high levels of Ca2+, and other pro-apoptotic factors (see Cassarino and Bennett for references). I showed that MPP+ opens the MTP in isolated mitochondria via an ROS-dependent mechanism. I also showed, via membrane potential measurements, that the activity of the MTP is increased in Alzheimer's and Parkinson's disease cybrids. Furthermore, I showed that the neuroprotective transcription factor, NF-kappaB, as well as the apoptosis cascade caspase proteins, are activated in our model systems.

Overall, I believe that my work has made significant contributions to our understanding of the role of mitochondria in neurodegenerative disorders. Specifically, I examined how mitochondrial defects, both genetically- and pharmacologically-derived, lead to alterations in cellular physiology relevant to cell death. These alterations include both protective nuclear responses, such as the antioxidant enzymes and NF-kappaB, and destructive mitochondrial responses, such as activation of the MTP, loss of membrane potential, and the release of cytochrome c, initiating the caspase cascade. Whether or not the cell ultimately capitulates to cell death most likely depends on the balance of these pro- and antiapoptotic responses.


CHEMICAL LOCALIZATION OF ACTIVATED
REACTIVE AND NEOPLASTIC ASTROCYTES

Morry D. Brown is also back on the wards, completing his clerkships. Morry recently received his Ph.D. in Neuroscience. His advisor is Dr. Scott VandenBerg. One of Morry's recent abstracts is below.

### The Regulation of Expression and Function of the Low Density Lipoprotein Receptor-Related Protein (LRP) in Diverse Neural Cell Subtypes.

The function of low density lipoprotein receptor-related protein (LRP), as a receptor mediating endocytosis in the central nervous system (CNS) is not well understood. My research addresses two hypotheses about LRP in the CNS: (1) that it is differentially regulated according to cell type; and (2) that altered expression affects the biologic activity of LRP-ligands at the cell surface and in the extracellular matrix. Immunofluorescence, cell surface binding, Northern and Western blot analyses demonstrated that LRP was differentially expressed in cultured astrocytic and neuronal cells. Receptor binding on viable cells, in addition to Northern and Western blot analyses, demonstrated that epidermal growth factor (EGF) decreased the level of LRP expression in all the glial cell lines, but not in cultured fetal human astrocytes (NHA).All tested neuronal cell lines were unaffected by similar treatments. Northern blot and nuclear run-on experiments showed that the reduced LRP in the glial tumor cells resulted from specifically decreased LRP mRNA transcription. Urokinase (uPA), as the model LRP ligand, and cell invasion, as the model biological activity, were analyzed to examine the effects of altered LRP expression. Western blots and uPA zymography of conditioned media showed that uPA was increased by conditions that decreased functional LRP: 1) EGF treatment, 2) receptor blocking with receptor associated protein (RAP), and 3) stable, anti-sense mRNA transfection. This increased uPA was associated with greater invasive migration of U-1242 MG glioblastoma cells in a fibrin barrier in a transwell culture system. Thus, LRP is tightly regulated in neural cells, and decreased LRP can affect biologic activity, as measured by cell invasion.

## Upcoming Events

**June 25-27** - Summer MD/PhD Retreat
Smith Mountain Lake, Wirtz, VA

**July 27** - Research In Progress Dinner

**August 17** -Research In Progress Dinner

**September** - Welcome Picnic for New Students, TBA

**September 21** - Research In Progress Dinner

**October 19** - Research In Progress Dinner

**November 11** - Annual Distinguished Speaker, Dr. Elaine Fuchs, Professor of Molecular Genetics and Cell Biology, University of Chicago

# Congratulations on Degrees Received

Claxton Baer, Ph.D., Neuroscience, January, 1999
"Structure-Function Analysis of Interphotoreceptor Retinoid-Binding Protein."

Morry Brown, Ph.D., Neuroscience, May, 1999
"The Regulation of Expression and Function of the Low Density Lipoprotein (LRP) in Diverse Neural Cell Subtypes."

David Cassarino, Ph.D., Neuroscience, January, 1999
"Mitochondrial Oxidative Stress and Nuclear Responses in Sporadic Neurodegenerative Diseases"

Wilbur Chang, Ph.D., Microbiology, May, 1999
"Class I Major Histocompatibility Complex Restricted T-lymphocyte Responses to Respiratory Syncytial Virus: An Analysis in Transgenic and Conventional Use."

Phillip Kuo, Ph.D., Physiology, May 1999
"The Mechanism of Coupled Proton Transport in the *Excherichia coli* $F_0F_1$ATP Synthase."

Kristen Jessen, Ph.D., Microbiology, May, 1999
"SNON Modulates Genes Regulating Growth and Differentiation."

Patty Steigerwald-Mullen, Ph.D., Microbiology, May, 1999
"Human Cellular Immune Responses to Epstein-Barr Virus Latent Antigens."

# Research in Progress Dinners

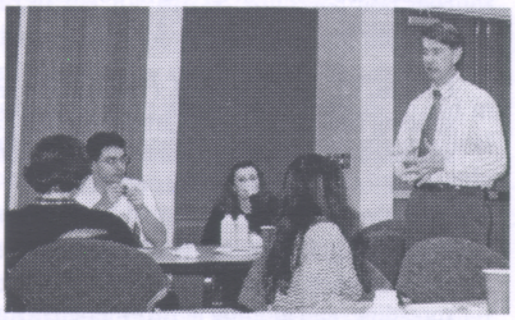
As new elements of our program, the monthly research in progress (RIP) dinners were established to gather students and faculty with diverse interests for the discussion of science. The result has been a smashing success. Set to the culinary styling of "Chef Ted," the RIPs debuted last year with discussions ranging from the presentation of MHC Class I restricted antigens to the role of retinol-binding-protein in retinal function. Led by senior MD/PhD students Claudio Mosse and Claxton Baer, each talk piqued the interest of students and faculty alike, setting the standard for future discussions.

In the months that followed, each RIP has been no less successful. The RIPs have served to highlight questions central to our understanding of science and its application to medicine. By discussing the projects of fellow students, the dinners have made us a more cohesive group and we look forward to RIPs in the future.

*-m.n.*

Carolyn Cronin, Mana Parast and Wilbur Chang enjoying dinner.

Mike Nemergut, expounding the virtues of the nuclear pore complex.



Gary Owens, welcoming all to the monthly dinner.

# 1998-1999 Publications by Current M.D./Ph.D. Students

*-s.c.*

**Baer, C.A.**, Retief, J.D., Van Niel, E., Braiman, M.S., and Gonzalez-Fernandez, F. (1998). Soluble expression in E. coli of a functional interphtoreceptor retinoid-binding protein module fused to thioredoxin: Correlation of vitmain A binding regions with conserved domains of C-terminal processing proteases. Exp.Eye Res. 66:249-262.

Gonzalez-Fernandez, F., **Baer, C.**, Van Niel, E., Braiman, M.S., Okajima, T.L., and Pepperberg, D.R. (1998). Fourth module of Xenopus interphotoreceptor retinoid-binding protein: activity in retinoid transfer between the retinal pigment epithelium and rod photoreceptors. Curr.Eye Res. 17:1150-1157.

**Baer, C.A.**, Van Niel, E., Cronk, J.W., Kinter, M.T., Sherman, N.E., Braiman, M.S., Gonzalez-Fernandez, F. (1998). Arginine to glutamine substitutions in the fourth module of Xenopus interphotoreceptor retinoid-binding protein. Mol.Vis. 4:30.

**Cassarino D.S.**, Fall C.P., Smith T.S., Bennett J.P., Jr. (1998) Pramipexole reduces reactive oxygen species production in vivo and in vitro and inhibits the mitochondrial permeability transition produced by the parkinsonian neurotoxin methylpyridinium ion. J. Neurochem. 71:295-301.

**Cassarino D.S.**, Parks J.K., Parker W.D., Jr., Bennett J.P., Jr. (1998) The parkinsonian neurotoxin MPP+ opens the mitochondrial permeability transition pore and releases cytochrome c in isolated mitochondria via an oxidative mechanism. Biochim. Biophys. Acta. 1453:49-62.

**Cassarino D.S.**, Parks J.K., Swerdlow R.H., Parker, W.D., Jr., and Bennett, J.P., Jr. (1998). Cyclosporin A increases resting mitochondrial membrane potential in SY5Y cells and reverses the depressed mitochondrial membrane potential of Alzheimer's Disease cybrids. Biochem. Biophys. Res. Commun. 248:168-173.

**Cassarino D.S.**, and Bennett, J. P. (1999) Mitochondrial oxidative pathology, nuclear responses, and cell death in neurodegenerative diseases, Brain Research Reviews. 1:1-25.

Swerdlow R.H., Parks J.K., **Cassarino D.S.**, Trimmer P.A., Miller S.W., Maguire D.J., Sheehan J.P., Maguire R.S., Pattee G., Juel V., Phillips L.H., Tuttle J.B., Bennett J.P., Jr., Davis R.E., Parker W.D., Jr. (1998) Mitochondria in sporadic amyotrophic lateral sclerosis. Experimental Neurology, 153:135-142.

Swerdlow R.H., Parks J.K., Davis J.N., **Cassarino D.S.**, Trimmer P.A., Currie L.J., Doherty J., Bridges W.S., Bennett J.P., Jr., Wooten G.F., Parker W.D., Jr. (1998) Matrilinear inheritance of complex I dysfunction in a multigenerational Parkinson's disease family. Annals Neurol. 44:873-881.

*-continued on next pg.*

## Recent Publications *(continued)*

**Chen, M.S.**, Almeida, E.A.C., Huovila, A.-P. J. Takahashi, Y. Shaw, L.M. Mercurio, A. M. and J. M. White. (1999) Evidence that distinct "states" of the integrin alpha 6 beta 1 interact with laminin and an ADAM protein. J. Cell Biol. 144:549-561.

Coonrod, S. Naaby-Hansen, J. Shetty, H. Shibahara, **Chen, M.**, White J., and J. Herr. (1999) Treatment of mouse oocytes with PI-PLC releases 70 kDa (pI 5) and 35-45 kDa (pI 5.5) protein clusters from the egg surface and inhibits sperm-oolemma binding and fusion. Dev. Biol 207:334-349.

**Cronin, C.**, and Scrable H. (1998) Differential splicing and translation of artificial genes caused by sequences linking the promoter to the coding region.. Am J Hum Genetics 63: A37.

**Kirby, J.L.**, Lysiak, J.J., Sankovic, M., Otey, C.A., and Gonias, S.L., (1998). Altered adhesion, spreading, and motility in LRP-deficient murine embryonic fibroblasts (MEFs). Annual Meeting of the American Society for Cell Biology.

**Kuo, P.H.** and Nakamoto, R.K. (1998) Stability and Functionality of cysteine-less $F_OF_1$ ATP synthase from Escherichia Coli. FEBS Letters 426:217-220.

**Luckey, C.J.**, King, G.M., Marto, J.A., Venketeswaran, S., Maier, B.F., Crotzer, V.L., Colella, T.A., Shabanowitz, J., Hunt, D.F., and Engelhard, V.H. (1998) Proteasomes can either generate or destroy MHC class I epitopes: evidence for nonproteasomal epitope generation in the cytosol, Journal of Immunology, 161:112-121.

**Mosse, C.A.**, Meadows, L., **Luckey, C.J.**, Kittlesen, D.J., Huczko, E.L., Slingluff, C.L., Jr., Shabanowitz, J., Hunt, D.F., and Engelhard, V.H. (1998) The class I antigen processing pathway for the membrane protein tyrosinase involves translation in the endoplasmic reticulum and processing in the cytosol, Journal of Experimental Medicine, 187:37-48.

**Parast, M.**, and Otey, C. (1998) Identification of a novel protein that localizes to stress fibers and focal adhesions in fibroblasts and to Z-discs in cardiac myocytes." Mol. Biol. Cell. 9:269a.

**Schaenman, J.**, Driscoll, P., Hockensmith, J., Mann, B., and Petri, W. (1998) An upstream regulatory element containing two nine basepair repeats regulates expression of the *Entamoeba histolytica* hgl5 lectin gene" Molecular and Biochemical Parisitology 94:309-313.

---

## M.D./Ph.D. Program
## University of Virginia

Graduate Programs Office
#456, Health Sciences Center
Charlottesville, VA 22908

http://www.med.virginia.edu/ed-programs/gpo/mstp/mstp.html
medgpo16@virginia.edu
(804) 924-1294 (phone)
(804) 924-0140 (fax)